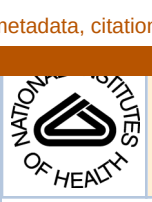

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Polymorphisms in oxidative stress genes, physical activity, and breast cancer risk

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Abstract

Purpose—The mechanisms driving the physical activity–breast cancer association are unclear. Exercise both increases reactive oxygen species production, which may transform normal epithelium to a malignant phenotype, and enhances antioxidant capacity, which could protect against subsequent oxidative insult. Given the paradoxical effects of physical activity, the oxidative stress pathway is of interest. Genetic variation in *CAT* or antioxidant-related polymorphisms may mediate the physical activity–breast cancer association.

Methods—We investigated the main and joint effects of three previously unreported polymorphisms in *CAT* on breast cancer risk. We also estimated interactions between recreational physical activity (RPA) and 13 polymorphisms in oxidative stress-related genes. Data were from the Long Island Breast Cancer Study Project, with interview and biomarker data available on 1,053 cases and 1,102 controls.

Results—Women with ≥1 variant allele in *CAT* rs4756146 had a 23 % reduced risk of postmenopausal breast cancer compared with women with the common TT genotype (OR = 0.77; 95 % CI = 0.59–0.99). We observed two statistical interactions between RPA and genes in the anti-oxidant pathway (p = 0.043 and 0.006 for *CAT* and *GSTP1*, respectively). Highly active women harboring variant alleles in *CAT* rs1001179 were at increased risk of breast cancer compared with women with the common CC genotype (OR = 1.61; 95 % CI, 1.06–2.45). Risk reductions were observed among moderately active women carrying variant alleles in *GSTP1* compared with women homozygous for the major allele (OR = 0.56; 95 % CI, 0.38–0.84).

Conclusions—Breast cancer risk may be jointly influenced by RPA and genes involved in the antioxidant pathway, but our findings require confirmation.

Keywords

Breast cancer; Epidemiology; Catalase; Physical activity; Oxidative stress

Introduction

Oxidative stress is hypothesized to play an important role in breast carcinogenesis [1–4] and is caused by the imbalance of reactive oxygen species (ROS) production and antioxidant defenses which neutralize these molecules [5]. ROS may be generated through any number of endogenous or exogenous mechanisms. While modest levels of ROS are useful for cell signaling processes [6], excess production may result in DNA damage, lipid peroxidation, and protein modification [7–9]. When endogenous or exogenous ROS production occurs in an environment with sufficient *in vivo* defense mechanisms to scavenge the ROS, there are seemingly few harmful effects. When there is excess ROS production and/or insufficient defense mechanisms, oxidative stress may ensue. There are several antioxidant defenses that can protect against oxidative damage including catalase (*CAT*), manganese superoxide dismutase (*MnSOD*), glutathione peroxidase (*GPX*), glutathione *S*-transferases (*GSTs*), myeloperoxidase (*MPO*), and catechol-O-methyltransferase (*COMT*) [1]. CAT plays an important role in neutralizing ROS by converting H_2O_2 into H_2O and O_2 [1]. Activity levels of the CAT enzyme are likely affected by a functional polymorphism (rs1001179) in the promoter region of the gene [10]. While this polymorphism has been associated with decreased enzyme activity [11–14], its association with breast cancer risk is unclear [11, 15,

16]. Other polymorphisms in *CAT* may be important in understanding the underlying association with breast cancer incidence and should be considered.

While physical inactivity is a well-established risk factor for breast cancer [17], the mechanisms driving the association are not well described [18–20]. Given the biological adaptation of enhanced antioxidant enzymatic capacity that occurs with regular exercise and its contribution to ROS, the oxidative stress pathway may be of interest. Physical activity may therefore interact with antioxidant-related genetic polymorphisms to influence breast carcinogenesis. No previous epidemiologic investigations have explored this possibility. We hypothesized that genotypes related to reduced antioxidant expression may have an antagonistic effect on the benefits of physical activity. In this report, we aimed to: (1) examine the independent main effects of three variants in the *CAT* gene (rs4756146, rs2284365, and rs480575) on breast cancer risk; (2) examine two-way interactions between SNPs in the *CAT* gene and breast cancer risk; and (3) examine potential interaction between recreational physical activity (RPA) and several oxidative stress-related genes (*CAT*, *COMT*, *GPX*, *GSTA1*, *GSTM1*, *GSTP1*, *GSTT1*, *MnSOD*, and *MPO*) with respect to breast cancer incidence. Secondary aims were to evaluate associations between *CAT* polymorphisms and breast cancer with cases categorized according to tumor hormone receptor status. These aims were accomplished through the use of existing biomarker and questionnaire data from the Long Island Breast Cancer Study Project (LIBCSP).

Materials and methods

Study population

Study participants were from the LIBCSP, a population-based case–control study conducted among English-speaking female residents of Nassau and Suffolk counties, Long Island, New York. Details of the study methods have been described previously [21]. Briefly, LIBCSP cases were women aged 20–98 years diagnosed with a first primary *in situ* or invasive breast cancer between 1 August 1996 and 31 July 1997. Case women were identified through daily or weekly contact with local hospital pathology departments. Population-based controls were women without a personal history of breast cancer randomly selected using random digit dialing for those under age 65 and the Health Care Finance Administration rosters for women aged 65 and older. Controls were frequency-matched to the expected age distribution of case women by 5-year age groups. All data were collected through a 2-h, interviewer-administered, structured questionnaire. Interview response among eligible cases and controls were 82.1 % (n = 1,508) and 62.8 % (n = 1,556), respectively. Respondents were more likely to be older (median age = 57 years in cases and 56 years in controls), post-menopausal (n = 1,003 cases and 989 controls), and white (93.4 % white, which reflects the underlying distribution of the source population).

Of those who completed an interview, 73.1 % of cases and 73.3 % of controls donated a blood sample. Among women who donated blood, genotyping was unavailable for 4.4 % of cases and 3.4 % of controls primarily due to insufficient DNA. Our final sample therefore includes 1,053 cases and 1,102 controls. Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the collaborating institutions.

SNP selection and genotyping

We selected three SNPs in *CAT* for genotyping (rs4756146, rs2284365, and rs480575). A tagging strategy was employed to maximize our ability to capture genetic variation across the *CAT* gene (gene and 1,000 bp upstream and downstream). Tag SNPs were selected using the SNPinfo web server from the National Institute of Environmental Health Science

[22] based on data from phase I and II of the International HapMap Project database [23]. Given the racial homogeneity of the LIBCSP population with DNA available for the proposed analyses [24], the CEU population (30 Utah trios with ancestry from northern and western Europe) was used as the reference panel for SNP selection. We imposed a minor allele frequency (MAF) cutoff value of 10 % and r^2 threshold minimum of 0.80 on SNP selection procedures. From the 11 tag SNPs identified to capture the CAT region, three were singleton or double bins, two had MAF <10 %, and one was previously genotyped in LIBCSP. Of the remaining five tag SNPs, we selected three based on location, bin size, and linkage disequilibrium with functional variants.

In addition to the newly genotyped *CAT* variants, we selected 10 functional polymorphisms from nine genes in the oxidative stress pathway to assess gene*environment (G*E) interactions with RPA: *CAT* (rs1001179), *COMT* (rs4680 and rs737865), *GPX* (rs1050450), *GSTA1* (rs3957356), *GSTM1* (gene deletion), *GSTP1* (rs1695), *GSTT1* (gene deletion), *MnSOD* (rs4880), and *MPO* (rs2333227). A single base pair change affecting polyphen prediction (*GPX*), transcription factor binding prediction (*CAT*, *COMT* rs737865, *MNSOD*, and *GSTA1*), miRNA binding (*GPX*), 3D conformation (*COMT* rs4680), or splicing regulation (*GPX*, *COMT* rs4680, *MPO*, and *GSTP1*) were defined as potentially functional SNPs. Similarly, base pair changes that were non-synonymous (*GPX*, *COMT* rs4680, *MPO*, and *GSTP1*) or resulted in a stop codon were also classified as potentially functional. These polymorphisms were identified through the breast cancer literature and the SNPinfo web server [22]. The main effects of these associations with breast cancer risk have been previously reported in the LIBCSP study population [11, 25–30]. However, interactions with physical activity have not been considered. Previously published SNP-specific effects among postmenopausal women for the genes of interest are provided to offer a full pathway context for our findings on the effect of RPA and ROS-related polymorphisms.

A non-fasting 40 mL blood sample was obtained from participants at the time of interview and shipped at room temperature, overnight, for processing. Genomic DNA was extracted from mononuclear cells in whole blood separated by Ficoll (Sigma Chemical Co., St. Louis, Missouri). Pelleted cells were frozen at −80 °C until DNA isolation by standard phenol, and chloroform isoamyl alcohol extraction and RNase treatment were performed [21]. Genotyping of newly selected *CAT* SNPs was accomplished using Taqman assays (Applied Biosystems, Foster City, CA) in 384-well plates. For the remaining SNPs, genotyping was performed by BioServe Biotechnologies (Laurel, MD) using Sequenom's high-throughput matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, as described previously [30]. Controls for genotype and two non-template controls were included on each plate. Samples that were outside the variables defined by the controls were identified as non-informative and retested. For quality control, 10 % of samples were distributed throughout the DNA samples as blinded duplicates. Laboratory personnel were blinded to case–control status, and all genotyping results were reviewed manually.

Recreational physical activity and covariate assessment

Exposure information was obtained from two sources: the interviewer-administered structured questionnaire and laboratory analyses using blood samples to obtain genotypes for *CAT* and oxidative stress genes. As part of the structured questionnaire, participants were asked about their involvement in RPA using a modified instrument developed by Bernstein and colleagues [31]. Women were asked about all activities in which they had engaged for at least 1 h per week and 3 months or more in any year over the life course. Women who reported never having participated in activity were classified as having no RPA. Among ever RPA participators, information on the activity name, the ages the activity was started and stopped, and the number of hours per week and months per year the activity was performed was obtained. Activity data for ever participators were summed across all

activities for each year of a woman's life, providing a lifetime composite score of exercise duration from menarche (left truncated) to reference date. We previously reported the main effects of RPA during four etiologically relevant time periods (adolescent, reproductive, postmenopausal, and lifetime RPA) [32]. For the present analyses, we assessed the interaction between polymorphisms in oxidative stress genes and two time periods for which the effects for breast cancer were strongest: postmenopausal and lifetime RPA. Given our previous analysis showed no substantial differences by intensity [32], we report RPA using average hours only.

During the interviewer-administered structured questionnaire, participants were additionally queried about their demographic characteristics; reproductive, medical, and environmental histories; cigarette smoking and alcohol use; use of exogenous hormones; energy intake; and select anthropometric measurements. Among eligible cases, clinical data on the characteristics of their breast cancer diagnosis, including hormone receptor (HR) status, were obtained from medical records.

Statistical methods

We first conducted tests for Hardy–Weinberg equilibrium (HWE) using observed genotype frequencies among Caucasian controls and X^2 test with one degree of freedom [33]. Unconditional logistic regression [34] was used to estimate odds ratios (ORs) and 95 % confidence intervals (CIs) for the independent effects of *CAT* SNPs, their interactions, and the joint effect of oxidative stress variants and RPA. All *CAT* SNPs were initially evaluated using a general genetic model, but due to sparse data among women with the homozygous variant genotype, a dominant model (at least one variant allele vs. no variant alleles) was used for the analyses of main effects and subsequent interactions.

We identified potential confounders based on the known epidemiology of breast cancer and analysis of causal diagrams [35]. For *CAT* variants, potential confounders were first degree family history of breast cancer (yes/no), race (categorical), and religion (categorical). As reported in our recently published manuscript [32] that examines effects for RPA on breast cancer incidence, we considered the following potential confounders: education (categorical), family history of breast cancer (yes/no), history of benign breast disease (yes/no), income (categorical), lactation history (ever/never), use of oral contraceptives (ever/never), parity (categorical), and smoking history (never, current, former). Confounders were included in the final model if their inclusion changed the exposure estimate by greater than 10 % [36]. None of the above covariates met our criterion (which is consistent with the lack of confounding noted in our previous examination of the main effect of physical activity on breast cancer risk [32]). Additionally, adjustment for body mass did not alter our estimate by greater than 10 %. Final models were therefore adjusted only for 5-year age group.

The main effect of *CAT* variants on breast cancer risk was assessed among all women and within strata of menopausal status when the Breslow–Day p for homogeneity was <0.10 [37]. The effect of each *CAT* variant was evaluated by HR status stratifying cases into two groups using information on estrogen receptor (ER) and progesterone receptor (PR) status [38]: women with tumors that showed any hormone responsiveness (ER+/PR+, ER+/ PR−, and ER−/PR+) and women who showed none (ER−/PR−).

We evaluated potential G*E interactions (both additive and multiplicative) by using indicator terms for those with the genotype only, exposure only, and both the genotype and exposure of interest. For genotype, we assessed interactions using a dominant genetic model and for RPA, we classified participants into three categories with cut points based on the median value among controls: no RPA, low RPA (<control median), and high RPA (≥control median). Departures from the multiplicative null were assessed using the

likelihood ratio test, comparing a model with and without the interaction terms [37]. Departures from the additive null were estimated by the interaction contrast ratio (ICR). The magnitude of the additive interaction effect was estimated based on the following formula: ICR = OR11–OR01–OR10+1 and its respective confidence interval obtained by ICR ± 1.96 SE (ICR) [39]. If the relative risk, as approximated by the OR, for both genotype and exposure differed significantly from the relative risk of either factor alone added together minus 1, we concluded that there was evidence of additive interaction [40]. All analyses were conducted using SAS 9.1 (Cary, NC).

Results

HWE

Among Caucasian controls, the MAF for *CAT* SNPs rs4756146 C-, rs2284365 C-, and rs480575 G-alleles were 14, 25, and 31 %, respectively. Allele frequencies were comparable with those of the CEU HapMap population (8, 20, and 30 %), although control genotype distributions for rs4756146 ($p = 0.02$) and rs2284365 ($p = 0.01$) deviated significantly from HWE. Call rates were >95 % for *CAT* SNPs and we observed good agreement in the randomly selected duplicates included for quality control (*n* discordant for rs4756146 [$n = 3$, 8.6 %] and rs2284365 [$n = 0$, 0 %]) suggesting that deviation from HWE was not due to genotyping error.

Main SNP effects

The genotype frequencies and age-adjusted associations with breast cancer risk for *CAT* polymorphisms are reported in Table 1. We observed no substantial associations between the *CAT* SNPs rs4756146, rs2284365, or rs480575 and breast cancer risk when genes were examined individually. However, the Breslow–day test for homogeneity revealed modification by menopausal status for rs4756146 ($p = 0.0419$): strongest effects were observed among postmenopausal women; those with CT or CC genotypes had decreased risk of breast cancer compared with women with TT genotypes (OR = 0.77; 95 % CI, 0.59–0.99) (Table 2). We observed a non-significant increase in risk of breast cancer among premenopausal women carrying at least one variant allele (OR = 1.27; 95 % CI, 0.88–1.85). We also found some suggestion of difference in the effect of rs4756146 by HR status. There was an 11 % risk reduction among pre- and postmenopausal HR positive cases combined (OR = 0.89; 95 % CI, 0.69–1.15) and a 34 % risk reduction among HR negative cases (OR = 0.66; 95 % CI, 0.40–1.08) compared with all controls. There was no modification by family history or religion for any SNP, and no heterogeneity by menopausal status or across tumor types for *CAT* rs2284365 and *CAT* rs480575 (data not shown). Our results did not vary upon restriction to Caucasian women.

SNP–SNP interactions

We assessed all potential multiplicative interactions between the three newly genotyped *CAT* polymorphisms described above and a functional *CAT* polymorphism (rs1001179) previously reported by Ahn and colleagues [11]. Of the six possible two-way combinations, we found only one potential interaction between rs480575 and rs2284365 ($p = 0.087$), although this interaction did not reach statistical significance (a priori $\alpha = 0.05$). We observed a significantly decreased risk of breast cancer among women who carried at least one variant allele for *CAT* rs480575 and were homozygous for common alleles for *CAT* rs2284365 (OR = 0.69; 95 % CI, 0.49–0.96).

Gene–environment (GxE) interactions

The OR (95 % CI) for breast cancer risk by genotype and RPA are shown in Table 3 along with previously reported postmenopausal age-adjusted main effects for RPA and genetic variants. While we observed similar GxE results for lifetime RPA among all women, the effects were stronger once restricted to postmenopausal participants. This is likely due to the strength of the main effect as we previously found stronger inverse associations for postmenopausal RPA than lifetime RPA [32]. Models are therefore presented among postmenopausal women, using reduced variables for RPA (none, <control median, ≥control median) and a dominant genetic model.

The association between postmenopausal breast cancer risk and carrying at least one variant *CAT* allele (rs1001179; CT and TT genotypes) was increased among women who had engaged in >9.23 h/week of RPA from menopause to reference date (OR = 1.61; 95 % CI, 1.06–2.45; p for multiplicative interaction = 0.043). There was a modest risk reduction (OR = 0.89; 95 % CI, 0.59–1.34) among women who were heterozygous or homozygous for the variant allele and moderately active (0.01–9.23 h/week). Despite the significant interaction, the estimate in the no activity group was 1.36 (95 % CI, 0.83–1.21). We observed a significant 44 % risk reduction (OR = 0.56; 95 % CI, 0.38–0.84) among postmenopausal women who engaged in low to moderate RPA with at least one G allele (AG and GG combined) in *GSTP1* Ile105Val compared with those with the AA genotype (p for multiplicative interaction = 0.006). Among highly active women, there was little effect of genotype on breast cancer risk (OR = 1.08; 95 % CI, 0.71–1.64). There was some suggestion of an inverse association between the TC and CC genotypes of *CAT* SNP rs4756146 and postmenopausal breast cancer risk among non-active women (OR = 0.57; 95 % CI, 0.33–0.98), however, we observed no significant interaction on the multiplicative scale for this or any of the remaining SNP–RPA combinations. Stratum specific effects of genotype were also assessed using splines for RPA. These analyses revealed similar results as our categorical classification of RPA (data not shown). Additionally, our models did not support the presence of an additive interaction between any of the 13 polymorphisms and RPA (data not shown).

Discussion

In this population-based study, women with at least one variant allele in *CAT* rs4756146 had a 23 % reduced risk of postmenopausal breast cancer compared with women with the common TT genotype. The association was not observed among premenopausal women, or when both pre-and postmenopausal women were considered together. Examination of potential interactions between *CAT* SNPs revealed a significantly decreased risk of breast cancer among women who carried at least one variant allele for rs480575 and were homozygous for common alleles for rs2284365, although test of formal interaction was not significant. When we examined joint effects of polymorphisms in oxidative stress genes and RPA from menopause to reference date in relation to postmenopausal breast cancer risk, we found some evidence for modification of genotype effect by activity level. A non-statistically significant positive association was observed among women with more than one variant *CAT* allele (rs1001179). This association was stronger and statistically significant among participants who were highly active. The inverse association between *GSTP1* Ile105Val and breast cancer was more pronounced among women who were moderately active. These findings could indicate that lower neutralization of ROS may augment breast cancer risk among a background of high RPA, whereas higher enzymatic activity may result in enhanced risk reduction among women who are moderately physically active. However, given the lack of evidence across other oxidative stress markers these results require additional confirmation.

There are multiple reports of the association between the functional catalase-262 C/T polymorphism and breast cancer incidence in the epidemiologic literature [11, 15, 16], but no study to date has assessed the individual or combined effects of *CAT* tag SNPs (rs4756146, rs2284365, rs480575) and breast cancer risk. We found that the association among women carrying at least one variant allele in *CAT* SNP rs4756146 varied by menopausal status. While the exact mechanisms need to be further investigated, it is possible that postmenopausal women (with a lower estrogen milieu) may more greatly benefit from ROS removal. Given the important role of *CAT* in neutralizing ROS [1], polymorphisms resulting in reduced enzyme activity may alter an individual's ability to counter lipid peroxidation and DNA oxidation thereby influencing cancer risk. However, in light of the marginally significant odds ratios and little evidence for association among the remaining polymorphisms, these results may be due to chance.

Many [11, 15, 27, 30], but not all [29], studies which examined the association between ROS-related exposures, genotype, and breast cancer risk have shown that both ROS-generating (e.g., cigarette smoking and exogenous hormones) and ROS-opposing factors (e.g., consumption of fruits and vegetables) may interact with endogenous sources of pro- and antioxidants to modify the effects of oxidative stress-related genetic polymorphisms on breast cancer risk. Given the more complex physiological effects of physical activity, any interactions with SNPs in the oxidative stress pathway may be challenging to disentangle.

Physical activity is a known inducer of ROS [41–43] and has been associated with lipid peroxidation among trained athletes [44–46]. The seemingly paradoxical inverse association between physical activity and breast cancer risk may be explained, in part, by the long-term effects of regular exercise. Some studies suggest that while exercise-induced ROS production may be an immediate systemic response to physical activity, the lasting effect of regular exercise training is adaptation of antioxidant capacity [47, 48]. Regular activity has been shown to enhance antioxidant status at multiple levels in both animal models and clinic studies [49–53] and may render cells more resistant to subsequent oxidative insult [5] thereby neutralizing the potentially mutagenic effects of lipid peroxidation [49]. Changes in antioxidant status are proposed to occur even with moderate activity, which parallels our knowledge of the association between physical activity and breast cancer.

We previously reported a non-linear dose response association between RPA and breast cancer risk among postmenopausal women in the LIBCSP [32]. While a significant 30 % risk reduction was observed among women in the third quartile of activity (OR = 0.70; 95 % CI, 0.52–0.95) women in the highest quartile experienced a modest 16 % risk reduction (OR = 0.84, 95 % CI, 0.63–1.13). Our finding was contrary to many previous epidemiologic studies, which report an inverse dose-response association between physical activity and breast cancer risk [17]; however, the high levels of activity reported by women in the LIBCSP permitted us to consider a wider range of effects than prior investigations. One possible explanation for inconsistent findings among highly active women may be the presence of modification by biologically relevant genotypes. While the effect estimates for RPA in quartiles 3 and 4 were not substantially different one could posit that ROS induction among women with very high activity levels could be amplified by reduced antioxidant capacity in relevant genes such as *CAT.* Moreover, moderate levels of RPA may enhance risk reduction among women who are carriers of alleles known to be related to higher endogenous enzymatic activity such as the *GSTP1* Ile105Val variant [54–56]. Although there is a strong biologic rational for the role of exercise in oxidative stress, the lack of modification across other genes may suggest that the observed results are due to chance and should be interpreted with caution.

The effects observed in this study may be due to biases arising from sample selection, errors in recall, or mis-classification of genotype. In the LIBCSP, blood donation varied by both age and race [21]. While genotype is likely associated with race, given the small number of non-white women (6.6 % non-white) included in our study, racial variations in blood donation is likely negligible. Moreover, analyses restricted to Caucasian women resulted in little change to observed estimates. Inaccurate recall of exposure variables can similarly lead to biased results and is common in case–control studies. However, it is unlikely that misclassification of RPA is differential with respect to genotype. We therefore expect that recall differences by disease status would not substantially bias our interaction parameter estimates. Distributions of two *CAT* variants deviated significantly from HWE, which may inflate Type I error [57]. We anticipate that factors other than genotyping error (e.g., natural selection or non-random mating) may be responsible for the departure from HWE given the comparable allele frequency to the CEU HapMap population, the use of the high-throughput genotyping methods, as well as the high call and concordance rates. This study benefits from the relatively large sample size, which increased power to detect modest associations, perform subgroup analyses, and evaluate joint effects of genotype and RPA. However, even very large studies assessing main effects of genetic variants can quickly become underpowered when examining gene–environment interactions. Although the racial homogeneity of the LIBCSP population enhances internal validity, it is likely to reduce the generalizability of our study results. Despite potential racial variation in genotype frequency and exposure prevalence, we believe that this study may provide clues about the underlying biologic mechanisms of oxidative stress and RPA which are unlikely to vary by race.

In summary, variant alleles in rs4756146 appear to be associated with reduced breast cancer risk among post-menopausal women. The statistical interaction, on a multiplicative scale, between *CAT*, postmenopausal RPA, and breast cancer may support our biologically plausible hypothesis that ROS-generating risk factors act in combination with reduced antioxidant expression to increase the risk of breast cancer. Similarly, the observed interaction between *GSTP1* and RPA could suggest that ROS are best neutralized in environments where there is amplified anti-oxidant capacity either via endogenous or exogenous mechanisms. This study is, to our knowledge, the first to assess the interaction between oxidative stress genotypes and exercise. Our findings may support the link between physical activity, genetic polymorphisms in genes related to antioxidant capacity, and breast cancer risk, but given the probability of chance findings, these hypotheses should be explored in other studies with adequate power and equally detailed exposure assessment. Although genotype is non-modifiable, it is encouraging to note that women who were moderately physically active had enhanced risk reduction when they were carriers of alleles related to higher enzymatic activity.

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Table 1

Age-adjusted odds ratios and 95 % confidence intervals for the association between catalase variants and breast cancer risk. The Long Island Breast Cancer Study Project (1996–1997)

		Cases (*n* = 1,053)		Controls (*n* = 1,102)		OR (95 % CI)[a]	
***Gene* (rs)**	**Genotype**	***n***	**%**	***n***	**%**		
CAT (rs4756146)	TT	774	77.87	809	75.82	1.00	Reference
	TC	201	20.22	229	21.46	0.93	(0.75, 1.16)
	CC	19	1.91	29	2.72	0.68	(0.37, 1.22)
	TC and CC	220	22.13	258	24.18	0.90	(0.74, 1.11)
CAT (rs2284365)	TT	589	59.43	610	57.22	1.00	Reference
	TC	344	34.71	371	34.80	0.98	(0.81, 1.18)
	CC	58	5.85	85	7.97	0.72	(0.50, 1.03)
	TC and CC	402	40.56	456	42.77	0.93	(0.78, 1.11)
CAT (rs480575)	AA	517	52.54	504	48.60	1.00	Reference
	AG	378	38.41	422	40.69	0.89	(0.74, 1.08)
	GG	89	9.04	111	10.70	0.78	(0.58, 1.06)
	AG and GG	467	47.45	533	51.39	0.87	(0.73, 1.04)

[a]Odds ratio (OR) and 95 % confidence interval (CI)

Table 2

Age-adjusted odds ratios and 95 % confidence intervals for the association between catalase SNP rs4756146 and breast cancer risk by menopausal status

Gene (rs)	Cases	Controls	OR (95 % CI)[a]	
CAT (rs4756146) premenopausal				
TT	241	282	1.00	Reference
CT	70	68	1.32	(0.89, 1.94)
CC	6	6	0.88	(0.27, 2.85)
CT and CC	76	74	1.27	(0.88, 1.85)
CAT (rs4756146) postmenopausal				
TT	514	491	1.00	Reference
CT	127	152	0.81	(0.62, 1.06)
CC	12	23	0.51	(0.25, 1.04)
CT and CC	139	175	0.77	(0.59, 0.99)

The Long Island Breast Cancer Study Project (1996–1997)

[a]Odds ratio (OR) and 95 % confidence interval (CI)

Table 3

Age-adjusted odds ratios and 95 % confidence intervals for multiplicative effects of oxidative stress SNPs and postmenopausal recreational physical activity on postmenopausal breast cancer risk

Gene (SNP) major/minor allele postmenopausal RPA (average h/week)[a]	Homozygous for major allele		At least one copy of minor allele			*p for interaction*
	Ca/Co[b]	Ref	Ca/Co	OR	(95 % CI)[c]	
CAT (rs4756146) T/C						
<0.01	133/104	1.00	33/44	0.57	(0.33, 0.98)	*0.126*
0.01–9.23	169/140	1.00	48/51	0.78	(0.49, 1.24)	
>9.23	137/163	1.00	36/45	1.05	(0.63, 1.76)	
CAT (rs2284365) T/C						
<0.01	104/80	1.00	64/69	0.70	(0.44, 1.13)	*0.331*
0.01–9.23	126/109	1.00	92/81	0.97	(0.65, 1.44)	
>9.23	104/117	1.00	64/89	0.87	(0.57, 1.35)	
CAT (rs480575) A/G						
<0.01	90/71	1.00	77/76	0.76	(0.48, 1.22)	*0.692*
0.01–9.23	107/85	1.00	104/98	0.83	(0.55, 1.24)	
>9.23	93/99	1.00	79/100	0.91	(0.60, 1.39)	
CAT (rs1001179) C/T[d]						
<0.01	103/95	1.00	70/53	1.36	(0.83, 2.21)	*0.043*
0.01–9.23	149/126	1.00	75/71	0.89	(0.59, 1.34)	
>9.23	100/143	1.00	82/69	1.61	(1.06, 2.45)	
COMT (rs4680) G/A[e]						
<0.01	46/37	1.00	128/116	0.81	(0.47, 1.40)	*0.446*
0.01–9.23	64/54	1.00	162/142	0.99	(0.64, 1.53)	
>9.23	56/52	1.00	130/160	0.78	(0.49, 1.23)	
COMT (rs737865) T/C[f]						
<0.01	89/77	1.00	80/76	0.97	(0.60, 1.56)	*0.439*
0.01–9.23	109/87	1.00	118/107	0.88	(0.59, 1.30)	
>9.23	77/98	1.00	102/114	1.11	(0.74, 1.68)	
GPX (rs1050450) C/T[g]						
<0.01	97/82	1.00	93/70	1.46	(0.92, 2.34)	*0.349*

Gene (SNP) major/minor allele postmenopausal RPA (average h/week)[a]	Homozygous for major allele		At least one copy of minor allele			*p for interaction*
	Ca/Co[b]	Ref	Ca/Co	OR	(95 % CI)[c]	
0.01–9.23	107/97	1.00	120/96	1.08	(0.73, 1.61)	
>9.23	79/103	1.00	103/109	1.18	(0.78, 1.79)	
GSTA1 (rs3957356) G/A[h]						
<0.01	49/48	1.00	124/104	1.11	(0.67, 1.84)	*0.295*
0.01–9.23	76/68	1.00	151/126	1.07	(0.71, 1.63)	
>9.23	59/61	1.00	124/152	0.84	(0.54, 1.30)	
GSTP1 (rs1695) A/G[i]						
<0.01	84/80	1.00	90/68	1.22	(0.77, 1.95)	*0.006*
0.01–9.23	123/80	1.00	97/109	0.56	(0.38, 0.84)	
>9.23	76/92	1.00	103/120	1.08	(0.71, 1.64)	
GSTM1 (Null vs. present)[j]						
<0.01	72/73	1.00	86/65	1.40	(0.86, 2.28)	*0.387*
0.01–9.23	105/99	1.00	111/78	1.38	(0.92, 2.08)	
>9.23	93/108	1.00	82/88	1.12	(0.73, 1.71)	
GSTT1 (Null vs. present)[k]						
<0.01	124/109	1.00	34/31	0.92	(0.51, 1.64)	*0.526*
0.01–9.23	175/136	1.00	42/42	0.78	(0.48, 1.28)	
>9.23	139/153	1.00	36/47	0.96	(0.58, 1.60)	
MnSOD (rs4880) T/C[l]						
<0.01	46/39	1.00	128/110	0.87	(0.51, 1.48)	*0.195*
0.01–9.23	59/57	1.00	164/138	1.17	(0.76, 1.81)	
>9.23	57/51	1.00	125/161	0.74	(0.47, 1.16)	
MPO (rs2333227) G/A[m]						
<0.01	105/95	1.00	69/57	1.16	(0.72, 1.87)	*0.119*
0.01–9.23	144/112	1.00	82/84	0.76	(0.51, 1.14)	
>9.23	109/136	1.00	74/76	1.16	(0.76, 1.76)	

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[a]Postmenopausal RPA ≤ 9.23 h/week (OR = 0.99; 95 % CI, 0.77–1.26) RPA >9.23 h/week (OR = 0.77; 95 % CI, 0.60–0.99)

[b] Cases (Ca) and controls (Co)

[c] Odds ratio (OR) and 95 % confidence interval (CI)

[d] Ahn et al. [26] Postmenopausal OR = 1.15; 95 % CI, 0.92–1.43 (Previous report used recessive model)

[e] Gaudet et al. [25] Postmenopausal OR = 0.90; 95 % CI, 0.70–1.14

[f] Gaudet et al. [25] Postmenopausal OR = 0.91; 95 % CI, 0.73–1.13

[g] Ahn et al. [26] Postmenopausal OR = 1.13; 95 % CI, 0.91–1.41

[h] Ahn et al. [27] Postmenopausal OR = 1.04; 95 % CI, 0.83–1.31

[i] Steck et al. [28] Postmenopausal OR = 0.93; 95 % CI, 0.74–1.15

[j] Steck et al. [28] Postmenopausal OR = 1.21; 95 % CI, 0.97–1.52

[k] Steck et al. [28] Postmenopausal OR = 0.92; 95 % CI, 0.70–1.21

[l] Gaudet et al. [29] Postmenopausal OR = 0.99; 95 % CI, 0.81–1.21

[m] Ahn et al. [30] Postmenopausal OR = 0.91; 95 % CI, 0.73–1.14 (Previous report adjusted for age, family history, and parity)